UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/863,606	05/23/2001	Julianna Lisziewicz	RGT 7028	2145

7590 12/31/2002

The Law Offices of Valerie E. Looper
77126 Lightfall Court
Columbia, MD 21044

EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/863,606	Lisziewicz et al.
Examiner	**Art Unit**
Michael C. Wilson	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 10, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above, claim(s) *"administering...and then" in claim 1, and 15-21* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-14* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Upon review of the restriction requirement sent 9-10-02, paper number 4, it is readily apparent that claim 2 was inadvertently omitted from Group III drawn to methods of administering a gene delivery complex, wherein the genetic material is DNA because claim 2 encompasses foreign genetic material that is DNA.

Applicant's election with traverse of Group III, in Paper No. 5 is acknowledged. The traversal is on the ground(s) that the advantage of the present invention is the administration of two divergent classes of materials in combination (a gene delivery complex and antiretroviral drug therapy). This is not found persuasive. Inventions I and III are related as subcombinations disclosed as usable together in a single combination. The subcombinations are distinct from each other if they are shown to be separately usable. See MPEP § 806.05(d). In the instant case, administering a gene delivery complex (Group I) has a separate utility because it is used to induce a CTL response against a retrovirus while administering antiretroviral drug therapy (Group III) is used to suppress viral replication. The burden required to search the two inventions together is undue as the structure of the genetic complex is materially separate than the antiretroviral drug therapy, the search for each is materially distinct and separate, and the breadth of each encompasses numerous divergent species (e.g. genetic material encompasses DNA or RNA, antiretroviral drug therapy encompasses protease inhibitors or reverse transcriptase inhibitors). Claim 1 requires administering antiretroviral drug therapy which implies administering the drug to

a patient, while at the same time claim 1 merely requires "administering a gene delivery complex..." which is not limited to a patient. Therefore, the inventions are also distinct because "administering a gene delivery complex..." encompasses *in vitro* embodiments while "administering an antiretroviral drug therapy..." does not.

Applicants argue that the invention is a therapeutic immunization. "That is, a way to use a vaccine to treat an already existing infection. All of the known, commercialized vaccines, including those for smallpox, rabies and anthrax, are preventive. That is they are used alone, without any related treatment, before an infection has developed." Applicants argument is misplaced because it does not provide any reasoning why the Groups should be recombined. Applicants argument is also incorrect. For example, Eder (US Patent 5,973,347) taught a therapeutic treatment for immunization against a viral infection comprising administering a virus neutralized with antibodies (see abstract).

The restriction requirement is deemed proper and is therefore made FINAL.

Claims 15-21 and the phrase "administering an antiretroviral drug therapy until viral replication is effectively suppressed, and then" in claim 1 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 5.

Upon responding to the instant office action, the claims must be amended to delete any non-elected subject matter from the pending claims. Failure to delete non-elected subject matter from the claims in response to the instant office action will be considered non-responsive.

Claims 1-14 are under consideration in the instant office action as they relate to administering a gene delivery complex, wherein the genetic material is DNA. Claim 2 is only being considered as it relates to genetic material that is DNA. The phrase "administering an antiretroviral drug therapy until viral replication is effectively suppressed, and then" in claim 1 has not been considered in writing the instant office action.

Claim Objections

The phrase "complex is DNA and one or more agents" (claim 8) is grammatically incorrect. Use of one (singular) and agents (plural) in combination is improper. Upon correcting the error, the species in the Markush group may also require correcting.

Claim Rejections - 35 USC § 112

2. Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 1-14 lack written description because the structure of the gene delivery complex that is "therapeutic" in the method claimed has not been adequately described. The specification teaches a complex comprising i) manosylated PEI and ii) DNA encoding an immunogenic HIV protein operably linked to a promoter. Administration of the complex to a host was followed by an increase in CD4 cells then a decrease in CD4 cells (pg 53). Such a result is not considered therapeutic because the overall result does not result in an increase in CD4 cells. In addition, it cannot be concluded that the gene complex caused the initial increase in CD4 cells because the experiment did not include controls - animals that did not receive drug therapy or the gene complex. It is possible that the drug therapy caused the increase observed. An adequate written description of a method of gene delivery that is therapeutic as claimed requires more than a mere statement that it is part of the invention; what is required is a description of the components used in the method that result in a therapeutic effect. In conclusion, the specification does not teach any genetic immunization that is therapeutic as claimed.

Claims 1-14 lack written description because the structure of the gene delivery complex that has "a specific affinity for a receptor on an antigen presenting cell" as broadly claimed has not been adequately described. Claim 11 lacks written description because the specification does not adequately describe any complex that has a "specific affinity for the mannose receptor." The specification does not define "affinity" and does not teach any gene complex that binds a receptor of an APC but not a receptor of other cells (i.e. fibroblasts, hepatocytes). For example, the specification contemplates using compounds that bind the mannose receptor in the complex

because mannose receptors are found on dendritic cells. However, the mannose receptor is also found on macrophages and does not have a specific affinity for antigen presenting cells (Stahl, Feb. 1998, Curr. Opin. Immunol., Vol. 10, pages 50-55; page 51, col. 2). Therefore, use of compounds having an affinity to the mannose receptor, such as mannosylated PEI, are not specific to APCs because they also bind to macrophages. While mannosylated-PEI may bind to the mannose receptor, the PEI component of mannosylated-PEI may also bind and be internalized via the asialoglycoprotein receptor (page 16, last sentence, of parent application 09/153198). Therefore, mannosylated-PEI may have an affinity to the asialoglycoprotein and not a "specific affinity to the mannose receptor" as in claim 11. An adequate written description of the complex that has the desired affinity to a receptor of an APC requires more than a mere statement that it is part of the invention; what is required is a description of the specific components of the complex that confer such an affinity to the complex. In conclusion, the specification does not teach that mannosylated-PEI has "specific" affinity to the mannose receptor or to APCs as claimed.

3. Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-14 are not enabled because the structure of the gene delivery complex that is "therapeutic" in the method claimed has not been adequately described.

The state of the art at the time of filing was that the combination of vector, promoter, route of administration, level of expression and target tissue required to obtain a therapeutic or prophylactic effect using gene therapy was unpredictable. Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the

efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

The state of the art regarding treating retroviral infection was unpredictable. Stricker (Medical Hypotheses, June 1997, Vol. 48, pages 527-9) teaches that attempts to develop a vaccine against HIV have been unsuccessful because HIV vaccines do not neutralize HIV (pg 527, last paragraph through all of pg 528). Overall, a lack of understanding about protective immunity to HIV in humans, the sequence variability of HIV and the rapid replication of HIV contribute the ineffectiveness of vaccines against HIV (Bangham, Nov. 29, 1997, Lancet, Vol. 350, pages 1617-1621; page 1617, top of col. 1).

The specification teaches a complex comprising i) manosylated PEI and ii) DNA encoding an immunogenic HIV protein operably linked to a promoter. Administration of the complex to a host after drug therapy was followed by an increase in CD4 cells then a decrease in CD4 cells (pg 53). Such a result is not considered therapeutic because the overall result does not result in a net increase in CD4 cells. In addition, it cannot be concluded that the gene complex caused the initial increase in CD4 cells because the experiment did not include controls - animals that did not receive drug therapy or the gene complex. The specification does not provide adequate guidance indicating the increase in CD4 was caused by the gene complex - the drug therapy could have caused the increase in CD4. For a method of therapeutic gene delivery against retroviral infection to be enabled, the specification must adequately describe the structure of the gene complex used in the method and the method of administration that results in a therapeutic effect. Without such

guidance it would require one of skill in the art undue experimentation to overcome the unpredictability in the art regarding gene therapy and retroviral therapy to determine the combination of elements required to obtain a therapeutic effect against retroviral infection using a gene delivery complex. Therefore, the specification does not enable therapeutic genetic immunization using a gene delivery complex as claimed.

Claims 1-14 are not enabled because the specification does not provide adequate guidance to determine any complex that has a "specific affinity for a receptor of an antigen presenting cell" as claimed.

The specification does not define "affinity" and does not teach any sugar, PEI, PEI derivative or mixture thereof that has a "specific affinity for a receptor on an antigen presenting cell". The art at the time of filing did not teach sugars, PEI, PEI derivatives or mixtures thereof that had a "specific affinity for a receptor on an antigen presenting cell." For example, the specification contemplates using the mannose receptor for entry into dendritic cells; however, the mannose receptor is also found on macrophages (Stahl, Feb. 1998, Curr. Opin. Immunol., Vol. 10, pages 50-55; page 51, col. 2). The specification also contemplates using mannosylated-PEI which binds to the mannose receptor; however, the PEI component of mannosylated-PEI may be internalized via the asialoglycoprotein receptor which is found on non-APCs (e.g. hepatocytes) (page 16, last sentence). The specification does not teach that mannosylated-PEI is specific to the mannose receptor on APCs and that the PEI component could not be used to bind the asialoglycoprotein receptor on a non-APC (e.g. hepatocyte). It would have required one of skill

in the art undue experimentation to determine agents that specifically bound to receptors on antigen presenting cells and not to other receptors. Therefore, agents having a "specific affinity" for receptors on antigen presenting cells are not enabled.

4. Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 11 are indefinite because the metes and bounds of gene delivery complexes having an "specific affinity to a receptor on an antigen presenting cell" or "specific affinity to a mannose receptor" cannot be determined. It is unclear how "specific" the affinity must be. It is unclear if the receptor must only be found on an antigen presenting cell. Overall, it is unclear whether the complex must be "specific" to the receptor or to the antigen presenting cell and how "specific" the affinity must be.

Claim 1 is indefinite because it is unclear how the "foreign genetic material" and the "non-viral vector" are related. It is unclear if two vectors are required, if the foreign genetic material is part of the vector or if the foreign genetic material is also the non-viral vector.

Claim 3 is indefinite because the scope of "reverse transcriptase dependent virus" cannot be determined. The phrase does not clearly set forth a genus of viruses. If applicants intend the phrase to mean retroviruses, then the claim should clearly set forth the genus as "retrovirus."

Claims 4-6 are indefinite because the metes and bounds of a "substantial portion" cannot be determined. The term is not defined in the specification and does not have an art recognized

meaning as it is a relative term. It is unclear how much of an integrase-defective HIV is a "substantial portion". Is a "substantial portion" relative to the integrase-defective HIV or to the HIV from which it was derived?

Claim 6 is indefinite because the metes and bounds of what applicants consider an "integrase negative mutant" cannot be determined. It is unclear if the gene has been deleted or merely that the gene is non-functional.

Claim 6 is indefinite because the metes and bounds of "dual-tropic primary isolate" cannot be determined. The phrase is not defined in the specification and does not have an art recognized meaning.

Claim 7 is indefinite because putting stop codons in "reading frames" as claimed does not clearly set forth the structure of the DNA. The stop codons are inserted into the coding region of the integrase gene. A codon in the reading frame is replaced with a stop codon. The metes and bounds of "reading frames" cannot be determined because the entire coding region is a reading frame. It appears as though applicants are using "reading frames" to mean codons.

Claim 8 is indefinite because the Markush Group is improper. Sugars, PEI, and PEI derivatives are not species that share a genus. The structure of sugars is materially distinct and separate than that of PEI or PEI derivatives. As such, the group is improper.

Claim 9 is indefinite because "sugar-modified polyethylenimine" does not clearly set forth the structure of the agent. It is unclear how the PEI is modified with sugar - it the sugar attached

or merely used to alter the structure of PEI without attaching. It is unclear whether the "sugar-modified polyethylenimine" further limits the PEI or the PEI derivative in claim 8.

Claim 10 is indefinite because it is unclear if glucose is further limiting the "sugars" or the "derivatives" of PEI in claim 8.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

5. Claims 1, 2, 8 and 11-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Boussif (1995, PNAS, Vol. 92, pages 7297-7301).

Boussif taught administering a complex comprising i) PEI and ii) plasmid DNA comprising a nucleic acid sequence encoding luciferase operatively linked to a promoter (page 7297, col. 2, second parag.). Luciferase is the "foreign genetic material" in claim 1. The plasmid is the "non-viral vector." PEI inherently has an "affinity" for the asialoglycoprotein receptor of dendritic and Langerhans cells. Applicants taught transfecting dendritic cells with PEI and

plasmid DNA (page 23, line 20, of parent application '198). The only difference between the complex of Boussif and the complex described in the instant application is that the plasmids encode different proteins. Claims 11 and 14 are included because the metes and bounds of complexes that have a "specific affinity" for the "mannose receptor" cannot be envisioned and the affinity of the complex taught by Boussif for the mannose receptor cannot be determined as the patent office does not have the means to test the affinity of PEI for the mannose receptor. Without evidence to the contrary, the PEI/plasmid complex taught by Boussif inherently has "specific affinity" for the mannose receptor as claimed. In conclusion, the method of Boussif is equivalent to the method claimed.

6. Claims 1, 2 and 8-14 are rejected under 35 U.S.C. 102(a) as being anticipated by Zanta (Nov.-Dec. 1997, Bioconjugate Chem., Vol. 8, page 839-844).

Provisional application 60/058933 does not describe "PEI derivatives". Therefore, the effective filing date of claims 8-11 as they relate to "PEI derivatives" is the filing date of parent application 09/153198, which is 9-15-98.

Zanta taught administering a complex comprising i) glycosylated PEI (PEI with glucose (PEI-glu) or galactose (PEI-gal)) (page 840, col. 1, parag. 1) and ii) DNA encoding luciferase (parag. 3). Luciferase is the "foreign genetic material" in claim 1. The plasmid is the "non-viral vector." PEI inherently has an "affinity" for the asialoglycoprotein receptor of dendritic and Langerhans cells. Applicants taught transfecting dendritic cells with a complex of i) PEI-glu or PEI-gal and ii) plasmid DNA (page 24, Table 1, #4 and #5, of parent application '153). The only

difference between the complex of Zanta and the complex disclosed by applicants is that the plasmids encode different proteins. Claims 11 and 14 are included because the metes and bounds of complexes that have a "specific affinity" for the "mannose receptor" cannot be envisioned and the affinity of the complex taught by Zanta for the mannose receptor cannot be determined as the patent office does not have the means to test the affinity of PEI for the mannose receptor. As such, the PEI/plasmid complex taught by Zanta inherently has "specific affinity" for the mannose receptor as claimed. In conclusion, the method of Zanta is equivalent to the method claimed.

7. Claims 1, 2, 8 and 10-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Behr (US Patent 6,013,240, Jan. 11, 2000).

Behr taught administering a complex comprising i) PEI, and ii) plasmid DNA comprising a nucleic acid sequence encoding luciferase operatively linked to a promoter suspended in 5% glucose (col. 12, lines 53-57). Luciferase is the "foreign genetic material" in claim 1. The plasmid is the "non-viral vector." PEI inherently has an "affinity" for the asialoglycoprotein receptor of dendritic and Langerhans cells. Glucose is the "agent" in claim 8. Claims 11 and 14 are included because the metes and bounds of complexes that have a "specific affinity" for the "mannose receptor" cannot be envisioned and the affinity of the complex taught by Behr for the mannose receptor cannot be determined as the patent office does not have the means to test the affinity of PEI for the mannose receptor. As such, the PEI/plasmid complex taught by Behr inherently has "specific affinity" for the mannose receptor as claimed. In conclusion, the method of Behr is equivalent to the method claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-4, 8 and 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adachi (1986, J. Virol., Vol. 59, pages 284-291) in view of Boussif (1995, PNAS, Vol. 92, pages 7297-7301).

Adachi taught transfecting NIH 3T3 cells and lymphoid cells (e.g. B-cells) with a plasmid encoding HIV (page 284, col. 2, 8 lines from the bottom; page 285, col. 1, Table 1, see Raji; page 289, Table 2, see NIH 3T3). Transfecting is equivalent to "administering a gene delivery complex" as claimed. Adachi did not teach transfecting the cells using PEI. However, at the time of filing Boussif taught transfecting cells using a complex comprising i) PEI and ii) plasmid DNA for transfecting eukaryotic cells (page 7297, col. 2, second parag.). A complete discussion of Boussif can be found above in the 102 rejection.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to transfect NIH 3T3 or lymphoid cells with the plasmid encoding HIV as taught by Adachi using PEI as taught by Boussif. Motivation is provided by Boussif who states PEI is used to transfect many eukaryotic cell type (page 7299, col. 2 parag. 2) and that PEI is one of the most efficient systems for delivering polynucleotides (page 7301, col. 1, 12).

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

9. Claims 1-4 and 8-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adachi (J. Virol. 1986, Vol. 59, pages 284-291) in view of Zanta (Nov.-Dec. 1997, Bioconjugate Chem., Vol. 8, page 839-844).

Provisional application 60/058933 does not describe "PEI derivatives" (claim 8). Therefore, the effective filing date of the claims as they relate to "PEI derivatives" is the filing date of parent application 09/153198, which is 9-15-98.

Adachi taught transfecting NIH 3T3 cells and lymphoid cells (e.g. B-cells) with a plasmid encoding HIV (pg 284, col. 2, 8 lines from the bottom; page 285, col. 1, Table 1, see Raji; pg 289, Table 2, see NIH 3T3). Adachi did not teach transfecting the cells using PEI-derivatives. However, Zanta taught transfecting a wide variety of cells, including NIH 3T3, using a complex comprising i) glycosylated PEI (PEI with glucose (PEI-glu) or galactose (PEI-gal)) (page 840, col. 1, parag. 1) and ii) DNA (parag. 3). A complete discussion of Zanta can be found above in the 102 rejection.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to transfect eukaryotic cells, specifically NIH 3T3 cells, with the plasmid encoding HIV as taught by Adachi using PEI-glu or PEI-gal taught by Zanta. One of ordinary skill in the art would have been motivated to use PEI-glu or PEI-gal to improve transfection of NIH 3T3 as compared to electroporation or calcium phosphate precipitation and to improve

transfection of the eukaryotic cells of Adachi expressing the asialoglycoprotein receptor as suggested by Zanta (page 843, col. 1, line 6).

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

10. Claims 1-4, 8 and 10-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adachi (1986, J. Virol., Vol. 59, pages 284-291) in view of Behr (US Patent 6,013,240, Jan. 11, 2000).

Provisional application 60/058933 does not describe using glucose in the complex (claim 10). Therefore, the effective filing date of claim 10 is the filing date of parent application 09/153198, which is 9-15-98.

Adachi taught transfecting NIH 3T3 cells and lymphoid cells (e.g. B-cells) with a plasmid encoding HIV (pg 284, col. 2, 8 lines from the bottom; page 285, col. 1, Table 1, Raji cell line; pg 289, Table 2, see NIH 3T3). Adachi did not teach transfecting the cells using "glucose". However, Behr taught transfecting cells using a complex comprising i) PEI, and ii) plasmid DNA comprising a nucleic acid sequence encoding luciferase operatively linked to a promoter suspended in 5% glucose (col. 12, lines 53-57; see 102 rejection above).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to transfect eukaryotic cells, specifically, NIH 3T3 cells, with the plasmid encoding HIV as taught by Adachi using PEI and glucose as taught by Behr. One of ordinary skill in the art at the time the invention was made would have been motivated to use PEI and

glucose in the method of Adachi to improve transfection as compared to without PEI and glucose (Behr, col. 12, Example 14). One of ordinary skill in the art at the time the invention was made would have been motivated to transfect the cells of Behr with the plasmid of Adachi to study HIV in brain cells.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

11. Claims 1-8 and 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adachi (1986, J. Virol., Vol. 59, pg 284-291) in view of Boussif (1995, PNAS, Vol. 92, pages 7297-7301) as applied to claims 1-4, 8 and 11-14, further in view of Cara (1995, Virol., Vol. 208, pg 242-248).

The combined teachings of Adachi and Boussif taught transfecting NIH 3T3 and lymphoid cells (e.g. B-cells) using a complex comprising i) PEI and ii) a plasmid encoding HIV (Adachi, page 284, col. 2, 8 lines from the bottom; page 285, col. 1, Table 1, Raji cell line; page 289, Table 2, see NIH 3T3; Boussif, page 7297, col. 2, second parag.; see 103 above). The combined teachings of Adachi and Boussif did not teach the HIV had a stop codon inserted into the integrase gene. However, Cara taught an HIV vector having a stop codon introduced into the integrase gene that was integrase defective (page 243, parag. 2).

Thus it would have been obvious to one of ordinary skill in the art at the time the invention was made to transfect cells using a complex comprising i) PEI and ii) a plasmid encoding a replication defective retrovirus as taught by the combined teachings of Adachi and

Boussif wherein the retrovirus was integrase defective as taught by Cara. One of ordinary skill would have been motivated to introduce a stop codon into the integrase gene of the retroviral vector of Adachi to obtain retroviral particles that did not integrate and to understand the requirement of integrase for replication in human primary cells as suggested by Cara (page 243, col. 1, line 8).

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

12. Claims 1, 3-9, 11-13, ~~23, 26-36~~ are rejected under 35 U.S.C. 103(a) as being unpatentable over Adachi (1986, J. Virol., Vol. 59, pages 284-291) in view of Zanta (Nov.-Dec. 1997, Bioconjugate Chem., Vol. 8, page 839-844) as applied to claims 1-4 and 8-14, further in view of Cara (1995, Virol., Vol. 208, pages 242-248).

The parent application does not describe "PEI derivatives". Therefore, the effective filing date of the claims as they relate to "PEI derivatives" is the filing date of parent application 09/153198, which is 9-15-98.

The combined teachings of Adachi and Zanta taught transfecting NIH 3T3 and lymphoid cells (e.g. B-cells) with a complex comprising i) PEI-glu or PEI-gal and ii) a plasmid encoding HIV (Adachi, pg 284, col. 2, 8 lines from the bottom; pg 285, col. 1, Table 1, see Raji cell line; pg 289, Table 2, see NIH 3T3; Zanta, pg 840, col. 1, parag. 1 and 3; see 103 above). The combined teachings of Adachi and Zanta did not teach the HIV had a stop codon inserted into the integrase

gene. However, at the time of filing Cara taught an HIV vector having a stop codon introduced into the integrase gene that was integrase defective (page 243, parag. 2).

Thus it would have been obvious to one of ordinary skill in the art at the time the invention was made to transfect cells using a complex comprising i) PEI-glu or PEI-gal and ii) a plasmid encoding a replication defective retrovirus as taught by the combined teachings of Adachi and Zanta wherein the retrovirus was integrase defective as taught by Cara. One of ordinary skill would have been motivated to introduce a stop codon into the integrase gene of the retroviral vector of Adachi to obtain retroviral particles that did not integrate and to understand the requirement of integrase for replication in human primary cells as suggested by Cara (page 243, col. 1, line 8).

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

13. Claims 1-8 and 10-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adachi (1986, J. Virol., Vol. 59, pg 284-291) in view of Behr (US Patent 6,013,240, Jan. 11, 2000) as applied to claims 1-4, 8 and 10-14, further in view of Cara (1995, Virol., Vol. 208, pg 242-248).

The parent application does not describe using glucose in the complex (claim 10). Therefore, the effective filing date of claim 10 is the filing date of parent application 09/153,198, which is 9-15-98.

The combined teachings of Adachi and Behr taught transfecting cells with a complex comprising i) PEI and ii) a plasmid encoding HIV in a 5% glucose solution used to transfect cells (Adachi, pg 284, col. 2, 8 lines from the bottom; pg 285, col. 1, Table 1, see Raji cell line; pg 289, Table 2, see NIH 3T3; Behr, col. 12, lines 53-57; see 103 above). The combined teachings of Adachi and Behr did not teach the HIV had a stop codon inserted into the integrase gene. However, at the time of filing Cara taught an HIV vector having a stop codon introduced into the integrase gene that was integrase defective (page 243, parag. 2).

Thus it would have been obvious to one of ordinary skill in the art at the time the invention was made to transfect cells using a complex comprising i) PEI and ii) a plasmid encoding a replication defective retrovirus and glucose as taught by the combined teachings of Adachi and Behr wherein the retrovirus was integrase defective as taught by Cara. One of ordinary skill would have been motivated to introduce a stop codon into the integrase gene of the retroviral vector of Adachi to obtain retroviral particles that did not integrate and to understand the requirement of integrase for replication in human primary cells as suggested by Cara (pg 243, col. 1, line 8).

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

The following prior art is being made of record and not relied upon because it is considered pertinent to applicant's disclosure:

The proceedings of the 3rd European conference on gene therapy of cancer, held from Sept. 11-13, 1997 at the University of Berlin, as supported by Diebold (Diebold et al., Advances in Experimental Med. and Biol., Oct. 1998, Vol. 451, pages 449-455). The preface of Advances in Experimental Med. and Biol., Oct. 1998, Vol. 451 (page v and vi) states that Vol. 451 contains the proceedings of the 3rd European conference on gene therapy of cancer.

At the conference Diebold taught a complex comprising i) mannosylated PEI (PEI-man), and ii) plasmid DNA comprising a nucleic acid sequence encoding luciferase operatively linked to a promoter used to transfect dendritic cells via the mannose receptor (page 452, line 10; page 453, line 13-18). While Diebold described using a complex comprising PEI-man and DNA encoding an immunogenic protein at least a year and two days prior to the filing date of the instant application (Sept. 15, 1998), the conference was in Germany. 102(a) and (b) requires that the information known in this country or published in this country or a foreign country prior. It does not appear that the information disclosed by Diebold was known in this country or published in any country until the publication of Advances in Experimental Med. and Biol., Vol. 451 in Oct. 1998. Therefore, the information disclosed by Diebold at the conference is not available under 102(a) or (b).

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 1-14 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,420,176. Although the conflicting claims are not identical, they are not patentably distinct from each other because the gene delivery complex in '176 is required for the method claimed in the instant invention.

16. Claims 1-14 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of copending Application No. 10/081922. Although the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scope.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL C. WILSON
PATENT EXAMINER